Complete Summary

GUIDELINE TITLE

Anthrax as a biological weapon, 2002: updated recommendations for management.

BIBLIOGRAPHIC SOURCE(S)

Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Gerberding J, Hauer J, Hughes J, McDade J, Osterholm MT, Parker G, Perl TM, Russell PK, Tonat K. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002 May 1;287(17):2236-52. [114 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
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IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Exposure to or infection with anthrax (Bacillus anthracis)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Infectious Diseases
Internal Medicine

Obstetrics and Gynecology
Pathology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To review and update consensus-based recommendations for medical and public health professionals following a Bacillus anthracis attack against a civilian population

TARGET POPULATION

Adults, pregnant women, children and immunosuppressed persons exposed to or infected with anthrax as a biological weapon

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis of Anthrax Infection

1. Evaluation of epidemiological trends
2. Radiologic study: chest radiograph and/or chest computed tomography for cases of inhalation anthrax
3. Clinical microbiology laboratory studies: gram stain of unspun peripheral blood smear and blood culture for inhalation anthrax; gram stain and culture of vesicular fluid for cutaneous anthrax
4. Additional laboratory studies: enzyme-linked immunosorbent assay for protective antigen, polymerase chain reaction performed by national reference laboratories
5. Postmortem examination

Vaccination

1. Anthrax vaccine, an inactivated cell-free product (Bioport Corp, Lansing, MI)

Treatment/Postexposure Prophylaxis

Anthrax infection in the contained casualty setting:

1. Initial therapy: Ciprofloxacin OR doxycycline AND 1 or 2 additional antimicrobials (adults, children, pregnant women, immunosuppressed persons)

Anthrax infection in mass casualty setting or postexposure prophylaxis:

1. Initial therapy: Ciprofloxacin (adults, children, pregnant women, immunosuppressed persons); Alternative therapy: Doxycycline and/or amoxicillin (adults); amoxicillin (children and pregnant women)

Infection control

1. Standard barrier isolation
2. Notification of hospital epidemiologist, state health department, local hospital microbiology laboratories
3. Disinfection (e.g., hypochlorite) of environmental surfaces
4. Proper burial or cremation

Decontamination

MAJOR OUTCOMES CONSIDERED

Therapeutic and vaccine efficacy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE databases were searched from January 1966 to January 2002, using the Medical Subject Headings anthrax, Bacillus anthracis, biological weapon, biological terrorism, biological warfare, and biowarfare. Reference review identified work published before 1966. Participants identified unpublished sources.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The first consensus statement, published in 1999, followed a synthesis of the information and revision of 3 drafts. The guideline developers reviewed anthrax literature again in January 2002, with special attention to articles following the anthrax attacks of 2001. Members commented on a revised document; proposed revisions were incorporated with the working group's support for the final consensus document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Five external reviewers are acknowledged in the guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse and the Working Group on Civilian Biodefense: In September 2001, Bacillus anthracis spores were sent to several locations in the United States via the U.S. Postal Service. Twenty-two confirmed or suspect cases of anthrax infection resulted. Eleven of these were

inhalational cases, of whom 5 died; 11 were cutaneous cases (7 confirmed, 4 suspected). In the updated guideline, these attacks are termed the anthrax attacks of 2001. The 2002 revised guideline presents new information based on the analysis of the anthrax attacks of 2001, including developments in the investigation of the anthrax attacks of 2001; important symptoms, signs, and laboratory studies; new diagnostic clues that may help future recognition of this disease; current anthrax vaccine information; updated antibiotic therapeutic considerations; and judgments about environmental surveillance and decontamination.

Diagnosis

Table 2, below, lists the epidemiology, diagnostic tests, microbiology, and pathology for a diagnosis of inhalational anthrax infection.

Table 2. Diagnosis of Inhalational Anthrax Infection*	
Epidemiology	Sudden appearance of several cases of severe acute febrile illness with fulminant course and death OR Acute febrile illness in persons identified as being at risk following a specific attack (e.g., those in the 2001 attacks: postal workers, members of the news media, and politicians and their staff)
Diagnostic studies	• Chest radiograph: widened mediastinum, infiltrates, pleural effusion • Chest computed tomographic scan: hyperdense hilar and mediastinal nodes, mediastinal edema, infiltrates, pleural effusion • Thoracentesis: hemorrhagic pleural effusions
Microbiology	• Peripheral blood smear: gram-positive bacilli on blood smear • Blood culture growth of large gram-positive bacilli with preliminary identification of Bacillus species[&]
Pathology	Hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis; DFA stain of infected tissues

*See Table 1 in the original guideline document for list of febrile illness symptoms and signs

[&]Most rapid assays are available only at laboratories participating in the Laboratory Response Network.

Given the rarity of anthrax infection, the first clinical or laboratory suspicion of an anthrax illness must lead to early initiation of antibiotic treatment pending

confirmed diagnosis and should provoke immediate notification of the local or state health department, local hospital epidemiologist, and local or state public health laboratory. In the United States, a Laboratory Response Network (LRN) has been established through a collaboration of the Association of Public Health Laboratories and the Centers for Disease Control and Prevention (CDC) (details are available at: http://www.bt.cdc.gov/LabIssues/index.asp). Currently 81 clinical laboratories in the Laboratory Response Network can diagnose bioweapons pathogens. Several preliminary diagnostic tests for Bacillus anthracis can be performed in hospital laboratories using routine procedures. Bacillus anthracis is a gram-positive, nonhemolytic, encapsulated, penicillin-sensitive, spore-forming bacillus. Confirmatory tests such as immuno-histochemical staining, gamma phage, and polymerase chain reaction assays must still be performed by special reference laboratories in the Laboratory Response Network.

The determination of individual patient exposure to Bacillus anthracis on the basis of environmental testing is complex due to the uncertain specificity and sensitivity of rapid field tests and the difficulty of assessing individual risks of exposure. A patient (or patients) seeking medical treatment for symptoms of inhalational anthrax will likely be the first evidence of a clandestine release of Bacillus anthracis as a biological weapon. The appearance of even a single previously healthy patient who becomes acutely ill with nonspecific febrile illness and symptoms and signs consistent with those listed in Table 1 in the original guideline document and whose condition rapidly deteriorates should receive prompt consideration for a diagnosis of anthrax infection. The recognition of cutaneous cases of anthrax may also be the first evidence of an anthrax attack.

The likely presence of abnormal findings on either chest x-ray film or chest computed tomography scan is diagnostically important. Although anthrax does not cause a classic bronchopneumonia pathologically, it can cause widened mediastinum, massive pleural effusions, air bronchograms, necrotizing pneumonic lesions, and/or consolidation. The result can be hypoxemia and chest imaging abnormalities that may or may not be clinically distinguishable from pneumonia. In the anthrax attacks of 2001, each of the first 10 patients had abnormal chest x-ray film results and each of 8 patients for whom computed tomography scans were obtained had abnormal results. These included widened mediastinum on chest radiograph and effusions on chest computed tomography scan. Such findings in a previously healthy patient with evidence of overwhelming febrile illness or sepsis would be highly suggestive of advanced inhalational anthrax.

The bacterial burden may be so great in advanced inhalational anthrax infection that bacilli are visible on Gram stain of peripheral blood, as was seen following the 2001 attacks. The most useful microbiologic test is the standard blood culture, which should show growth in 6 to 24 hours. Each of the 8 patients who had blood cultures obtained prior to initiation of antibiotics had positive blood cultures. However, blood cultures appear to be sterilized after even 1 or 2 doses of antibiotics, underscoring the importance of obtaining cultures prior to initiation of antibiotic therapy (J. Gerberding, oral communication, March 7, 2002). If the laboratory has been alerted to the possibility of anthrax, biochemical testing and review of colonial morphology could provide a preliminary diagnosis 12 to 24 hours after inoculation of the cultures. Definitive diagnosis could be promptly confirmed by a Laboratory Response Network laboratory. However, if the clinical laboratory has not been alerted to the possibility of anthrax, Bacillus anthracis

may not be correctly identified. Routine procedures customarily identify a Bacillus species in a blood culture approximately 24 hours after growth, but some laboratories do not further identify Bacillus species unless specifically requested. This is because the isolation of Bacillus species most often represents growth of the common contaminant Bacillus cereus. Given the possibility of future anthrax attacks, it is recommended that routine clinical laboratory procedures be modified, so Bacillus anthracis is specifically excluded after identification of a Bacillus species bacteremia unless there are compelling reasons not to do so. If it cannot be excluded then the isolate should be transferred to a Laboratory Response Network laboratory.

Sputum culture and Gram stain are unlikely to be diagnostic of inhalational anthrax, given the frequent lack of a pneumonic process. Gram stain of sputum was reported positive in only 1 case of inhalational anthrax in the 2001 series. If cutaneous anthrax is suspected, a Gram stain and culture of vesicular fluid should be obtained. If the Gram stain is negative or the patient is taking antibiotics already, punch biopsy should be performed, and specimens sent to a laboratory with the ability to perform immunohistochemical staining or polymerase chain reaction assays. Blood cultures should be obtained and antibiotics should be initiated pending confirmation of the diagnosis of inhalational or cutaneous anthrax.

Nasal swabs were obtained in some persons believed to be at risk of inhalational anthrax following the anthrax attacks of 2001. Although a study has shown the presence of Bacillus anthracis spores in nares of some monkeys following experimental exposure to Bacillus anthracis spores for some time after exposure, the predictive value of the nasal swab test for diagnosing inhalational anthrax in humans is unknown and untested. It is not known how quickly antibiotics make spore recovery on nasal swab tests impossible. One patient who died from inhalational anthrax had a negative nasal swab. Thus, the Centers for Disease Control and Prevention advised in the fall of 2001 that the nasal swab should not be used as a clinical diagnostic test. If obtained for an epidemiological purpose, nasal swab results should not be used to rule out infection in a patient. Persons who have positive nasal swab results for Bacillus anthracis should receive a course of postexposure antibiotic prophylaxis since a positive swab would indicate that the individual had been exposed to aerosolized Bacillus anthracis.

Antibodies to the protective antigen (PA) of Bacillus anthracis, termed anti-PA IgG, have been shown to confer immunity in animal models following anthrax vaccination. Anti-PA IgG serologies have been obtained from several of those involved in the 2001 anthrax attacks, but the results of these assays are not yet published. Given the lack of data in humans and the expected period required to develop an anti-PA IgG response, this test should not be used as a diagnostic test for anthrax infection in the acutely ill patient but may be useful for epidemiologic purposes.

Postmortem findings are especially important following an unexplained death. Thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy adult are essentially pathognomonic of inhalational anthrax. Hemorrhagic meningitis should also raise strong suspicion of anthrax infection. However, given the rarity of anthrax, a pathologist might not

identify these findings as caused by anthrax unless previously alerted to this possibility.

If only a few patients present contemporaneously, the clinical similarity of early inhalational anthrax infection to other acute febrile respiratory infections may delay initial diagnosis although probably not for long. The severity of the illness and its rapid progression, coupled with unusual radiological findings, possible identification of Bacillus anthracis in blood or cerebrospinal fluid, and the unique pathologic findings should serve as an early alarm. The index case of inhalational anthrax in the 2001 attacks was identified because of an alert clinician who suspected the disease on the basis of large gram-positive bacilli in cerebrospinal fluid in a patient with a compatible clinical illness, and as a result of the subsequent analysis by laboratory staff who had recently undergone bioterrorism preparedness training.

Vaccination

The U.S. anthrax vaccine, named anthrax vaccine adsorbed (AVA), is an inactivated cell-free product, licensed in 1970, and produced by Bioport Corp., Lansing, MI. The vaccine is licensed to be given in a 6-dose series. In 1997, it was mandated that all U.S. military active- and reserve-duty personnel receive it.

Current vaccine supplies are limited and the U.S. production capacity remains modest. Bioport is the single U.S. manufacturing facility for the licensed anthrax vaccine. Production has only recently resumed after a halt required the company to alter production methods so that it conformed to the U.S. Food and Drug Administration (FDA) Good Manufacturing Practice standard. Bioport has a contract to produce 4.6 million doses of vaccine for the U.S. Department of Defense that cannot be met until at least 2003 (D. A. Henderson, oral communication, February 2002).

The use of anthrax vaccine adsorbed (AVA) was not initiated immediately in persons believed to have been exposed to Bacillus anthracis during the 2001 anthrax attacks for a variety of reasons, including the unavailability of vaccine supplies. Subsequently, near the end of the 60-day period of antibiotic prophylaxis, persons deemed by investigating public health authorities to have been at high risk for exposure were offered postexposure anthrax vaccine adsorbed series (3 inoculations at 2-week intervals, given on days 1, 14, and 28) as an adjunct to prolonged postexposure antibiotic prophylaxis. This group of affected persons was also offered the alternatives of continuing a prolonged course of antibiotics or of receiving close medical follow-up without vaccination or additional antibiotics. This vaccine is licensed for use in the preexposure setting, but because it had not been licensed for use in the postexposure context, it was given under investigational new drug procedures.

The working group continues to conclude that vaccination of exposed persons following a biological attack in conjunction with antibiotic administration for 60 days following exposure provide optimal protection to those exposed. However, until ample reserve stockpiles of vaccine are available, reliance must be placed on antibiotic administration. To date, there have been no reported cases of anthrax infection among those exposed in the 2001 anthrax attacks who took prophylactic

antibiotics, even in those persons not complying with the complete 60-day course of therapy.

Preexposure vaccination of some persons deemed to be in high-risk groups should be considered when substantial supplies of vaccine become available. A fast-track program to develop recombinant anthrax vaccine is now under way. This may lead to more plentiful vaccine stocks as well as a product that requires fewer inoculations. Studies to evaluate intramuscular vs subcutaneous routes of administration and less frequent dosing of anthrax vaccine adsorbed are also under way. (J. Hughes, oral communication, February 2002.)

Therapy

Given the rapid course of symptomatic inhalational anthrax, early antibiotic administration is essential. A delay of antibiotic treatment for patients with anthrax infection even by hours may substantially lessen chances for survival. Given the difficulty in achieving rapid microbiologic diagnosis of anthrax, all persons in high-risk groups who develop fever or evidence of systemic disease should start receiving therapy for possible anthrax infection as soon as possible while awaiting the results of laboratory studies.

There are no controlled clinical studies for the treatment of inhalational anthrax in humans. Thus, antibiotic regimens commonly recommended for empirical treatment of sepsis have not been studied. In fact, natural strains of Bacillus anthracis are resistant to many of the antibiotics used in these empirical regimens for sepsis treatment, such as those regimens based on the extended-spectrum cephalosporins. Most naturally occurring Bacillus anthracis strains are sensitive to penicillin, which historically has been the preferred anthrax therapy. Doxycycline is the preferred option among the tetracycline class because of its proven efficacy in monkey studies and its ease of administration. Other members of this class of antibiotics are suitable alternatives. Although treatment of anthrax infection with ciprofloxacin has not been studied in humans, animal models suggest excellent efficacy. In vitro data suggest that other fluoroquinolone antibiotics would have equivalent efficacy although no animal data using a primate model of inhalational anthrax are available. Penicillin, doxycycline, and ciprofloxacin are approved by the Food and Drug Administration for the treatment of inhalational anthrax infection, and other antibiotics are under study. Other drugs that are usually active in vitro include clindamycin, rifampin, imipenem, aminoglycosides, chloramphenicol, vancomycin, cefazolin, tetracycline, linezolid, and the macrolides.

Reports have been published of a Bacillus anthracis vaccine strain that was engineered to resist the tetracycline and penicillin classes of antibiotics. Balancing considerations of treatment efficacy with concerns regarding resistance, the working group in 1999 recommended that ciprofloxacin or other fluoroquinolone therapy be initiated in adults with presumed inhalational anthrax infection. It was advised that antibiotic resistance to penicillin- and tetracycline-class antibiotics should be assumed following a terrorist attack until laboratory testing demonstrates otherwise. Once the antibiotic susceptibility of the Bacillus anthracis strain of the index case had been determined, the most widely available, efficacious, and least toxic antibiotic was recommended for patients requiring treatment and persons requiring postexposure prophylaxis. Since the 1999

consensus statement publication, a study demonstrated the development of in vitro resistance of an isolate of the Sterne strain of Bacillus anthracis to ofloxacin (a fluoroquinolone closely related to ciprofloxacin) following subculturing and multiple cell passage.

Following the anthrax attacks of 2001, the Centers for Disease Control and Prevention (CDC) offered guidelines advocating use of 2 or 3 antibiotics in combination in persons with inhalational anthrax based on susceptibility testing with epidemic strains. Limited early information following the attacks suggested that persons with inhalational anthrax treated intravenously with 2 or more antibiotics active against Bacillus anthracis had a greater chance of survival. Given the limited number of persons who developed inhalational anthrax, the paucity of comparative data, and other uncertainties, it remains unclear whether the use of 2 or more antibiotics confers a survival advantage, but combination therapy is a reasonable therapeutic approach in the face of life-threatening illness. Another factor supporting the initiation of combination antibiotic therapy for treatment of inhalational anthrax is the possibility that an engineered strain of Bacillus anthracis resistant to 1 or more antibiotics might be used in a future attack. Some infectious disease experts have also advocated the use of clindamycin, citing the theoretical benefit of diminishing bacterial toxin production, a strategy used in some toxin-mediated streptococcal infections. There are no data as yet that bear specifically on this question. Central nervous system penetration is another consideration; doxycycline or fluoroquinolone may not reach therapeutic levels in the cerebrospinal fluid. Thus, in the aftermath of the anthrax attacks, some infectious disease authorities recommended preferential use of ciprofloxacin over doxycycline, plus augmentation with chloramphenicol, rifampin, or penicillin when meningitis is established or suspected.

The Bacillus anthracis isolate recovered from patients with inhalational anthrax was susceptible to all of the antibiotics expected in a naturally occurring strain. This isolate showed an inducible beta-lactamase in addition to a constitutive cephalosporinase. The importance of the inducible beta-lactamase is unknown; these strains are highly susceptible to penicillin in vitro, with minimum inhibiting concentrations less than .06 micrograms/mL. A theoretical concern is that this sensitivity could be overcome with a large bacterial burden. For this reason, the Centers for Disease Control and Prevention advised that patients with inhalational anthrax should not be treated with penicillin or amoxicillin as monotherapy and that ciprofloxacin or doxycycline be considered the standards based on in vitro activity, efficacy in the monkey model, and Food and Drug Administration approval.

In a contained casualty setting (a situation in which a modest number of patients require therapy), the working group supports these new Centers for Disease Control and Prevention antibiotic recommendations (Table 3 in the original guideline document) and advises the use of intravenous antibiotic administration. These recommendations will need to be revised as new data become available.

If the number of persons requiring therapy following a bioterrorist attack with anthrax is sufficiently high (i.e., a mass casualty setting), the working group recognizes that combination drug therapy and intravenous therapy may no longer be possible for reasons of logistics and/or exhaustion of equipment and antibiotic supplies. In such circumstances, oral therapy may be the only feasible option

(Table 4 of the original guideline document). The threshold number of cases at which parenteral therapy becomes impossible depends on a variety of factors, including local and regional health care resources.

In experimental animals, antibiotic therapy during anthrax infection has prevented development of an immune response. This suggests that even if the antibiotic-treated patient survives anthrax infection, risk of recurring disease may persist for a prolonged period because of the possibility of delayed germination of spores. Therefore, the working group recommends that antibiotic therapy be continued for at least 60 days postexposure, with oral therapy replacing intravenous therapy when the patient is clinically stable enough to take oral medication.

Cutaneous anthrax historically has been treated with oral penicillin. For reasons articulated in the original guideline document, the working group recommends that oral fluoroquinolone or doxycycline in the adult dosage schedules described in Table 5 of the original guideline document be used to treat cutaneous anthrax until antibiotic susceptibility is proven. Amoxicillin is a suitable alternative if there are contraindications to fluoroquinolones or doxycycline such as pregnancy, lactating mother, age younger than 18 years, or antibiotic intolerance. For cutaneous lesions associated with extensive edema or for cutaneous lesions of the head and neck, clinical management should be conservative as per inhalational anthrax treatment guidelines in Table 3 in the original guideline document. Although previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days, the working group recommends treatment for 60 days postexposure in the setting of bioterrorism, given the presumed concomitant inhalational exposure to the primary aerosol. Treatment of cutaneous anthrax generally prevents progression to systemic disease although it does not prevent the formation and evolution of the eschar. Topical therapy is not useful.

In addition to penicillin, the fluoroquinolones and the tetracycline class of antibiotics, other antibiotics effective in vitro include chloramphenicol, clindamycin, extended-spectrum penicillins, macrolides, aminoglycosides, vancomycin, cefazolin, and other first-generation cephalosporins. The efficacy of these antibiotics has not yet been tested in humans or animal studies. The working group recommends the use of these antibiotics only to augment fluoroquinolones or tetracyclines or if the preferred drugs are contraindicated, not available, or inactive in vitro in susceptibility testing. Bacillus anthracis strains exhibit natural resistance to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime. Therefore, these antibiotics should not be used.

Pleural effusions were present in all of the first 10 patients with inhalational anthrax in 2001. Seven needed drainage of their pleural effusions, 3 required chest tubes. Future patients with inhalational anthrax should be expected to have pleural effusions that will likely require drainage.

Post Exposure Prophylaxis

Guidelines for which populations would require postexposure prophylaxis to prevent inhalational anthrax following the release of a Bacillus anthracis aerosol as a biological weapon will need to be developed by public health officials depending on epidemiological circumstances. These decisions would require

estimates of the timing, location, and conditions of the exposure. Ongoing case monitoring would be needed to define the high-risk groups, to direct follow-up, and to guide the addition or deletion of groups requiring postexposure prophylaxis.

There are no Food and Drug Administration-approved postexposure antibiotic regimens following exposure to a Bacillus anthracis aerosol. Therefore, for postexposure prophylaxis, we recommend the same antibiotic regimen as that recommended for treatment of mass casualties; prophylaxis should be continued for at least 60 days postexposure (Table 4 in the original guideline document). Preliminary analysis of U.S. postal workers who were advised to take 60 days of antibiotic prophylaxis for exposure to Bacillus anthracis spores following the anthrax attacks of 2001 showed that 2% sought medical attention because of concern of possible severe allergic reactions related to the medications, but no persons required hospitalization because of an adverse drug reaction. Many persons did not begin or complete their recommended antibiotic course for a variety of reasons, including gastrointestinal tract intolerance, underscoring the need for careful medical follow-up during the period of prophylaxis. In addition, given the uncertainties regarding how many weeks or months spores may remain latent in the period following discontinuation of postexposure prophylaxis, persons should be instructed to report immediately flulike symptoms or febrile illness to their physicians who should then evaluate the need to initiate treatment for possible inhalational anthrax. As noted above, postexposure vaccination is recommended as an adjunct to postexposure antibiotic prophylaxis if vaccine is available.

Management of Special Groups

Consensus recommendations for special groups as set forth within the original guideline document reflect the clinical and evidence-based judgments of the working group and at this time do not necessarily correspond with Food and Drug Administration-approved use, indications, or labeling.

Children. It has been recommended that ciprofloxacin and other fluoroquinolones should not be used in children younger than 16 to 18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in a small number of children. However, balancing these risks against the risks of anthrax caused by an engineered antibiotic-resistant strain, the working group recommends that ciprofloxacin be used as a component of combination therapy for children with inhalational anthrax. For postexposure prophylaxis or following a mass casualty attack, monotherapy with fluoroquinolones is recommended by the working group (Table 4 in the original guideline document).

The American Academy of Pediatrics has recommended that doxycycline not be used in children younger than 9 years because the drug has resulted in retarded skeletal growth in infants and discolored teeth in infants and children. However, the serious risk of infection following an anthrax attack supports the consensus recommendation that doxycycline, instead of ciprofloxacin, be used in children if antibiotic susceptibility testing, exhaustion of drug supplies, or adverse reactions preclude use of ciprofloxacin.

According to the Centers for Disease Control and Prevention recommendations, amoxicillin was suitable for treatment or postexposure prophylaxis of possible anthrax infection following the anthrax attacks of 2001 only after 14 to 21 days of fluoroquinolone or doxycycline administration because of the concern about the presence of a beta-lactamase. In a contained casualty setting, the working group recommends that children with inhalational anthrax receive intravenous antibiotics (Table 3 in the original guideline document). In a mass casualty setting and as postexposure prophylaxis, the working group recommends that children receive oral antibiotics (Table 4 in the original guideline document).

The U.S. anthrax vaccine is licensed for use only in persons aged 18 to 65 years because studies to date have been conducted exclusively in this group. No data exist for children, but based on experience with other inactivated vaccines, it is likely that the vaccine would be safe and effective.

Pregnant Women. Fluoroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals and small numbers of children. Animal studies have discovered no evidence of teratogenicity related to ciprofloxacin, but no controlled studies of ciprofloxacin in pregnant women have been conducted. Balancing these possible risks against the concerns of anthrax due to engineered antibiotic-resistant strains, the working group recommends that ciprofloxacin as part of combination therapy for treatment of inhalational anthrax (Table 3 in the original guideline document) The working group also recommends that pregnant women receive fluoroquinolones in the usual adult dosages for postexposure prophylaxis or monotherapy treatment in the mass casualty setting (Table 4 in the original guideline document). The tetracycline class of antibiotics has been associated with both toxic effects in the liver in pregnant women and fetal toxic effects, including retarded skeletal growth.

Balancing the risks of anthrax infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline can be used as an alternative to ciprofloxacin as part of combination therapy in pregnant women for treatment of inhalational anthrax. For postexposure prophylaxis or in mass casualty settings, doxycycline can also be used as an alternate to ciprofloxacin in pregnant women. If doxycycline is used in pregnant women, periodic liver function testing should be performed. No adequate controlled trials of penicillin or amoxicillin administration during pregnancy exist. However, the Centers for Disease Control and Prevention recommends penicillin for the treatment of syphilis during pregnancy and amoxicillin as a treatment alternative for chlamydial infections during pregnancy. According to Centers for Disease Control and Prevention recommendations, amoxicillin is suitable postexposure prophylaxis or treatment of inhalational anthrax in pregnancy only after 14 to 21 days of fluoroquinolone or doxycycline administration.

Ciprofloxacin (and other fluoroquinolones), penicillin, and doxycycline (and other tetracyclines) are each excreted in breast milk. Therefore, a breast-feeding woman should be treated or given prophylaxis with the same antibiotic as her infant based on what is most safe and effective for the infant.

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for anthrax among those who are immunosuppressed has not been

studied in human or animal models of anthrax infection. Therefore, the working group consensus recommends administering antibiotics in the same regimens recommended for immunocompetent adults and children.

Infection Control

There are no data to suggest that patient-to-patient transmission of anthrax occurs and no person-to-person transmission occurred following the anthrax attacks of 2001. Standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax infection, but the use of high-efficiency particulate air filter masks or other measures for airborne protection are not indicated. There is no need to immunize or provide prophylaxis to patient contacts (e.g., household contacts, friends, coworkers) unless a determination is made that they, like the patient, were exposed to the aerosol or surface contamination at the time of the attack.

In addition to immediate notification of the hospital epidemiologist and state health department, the local hospital microbiology laboratories should be notified at the first indication of anthrax so that safe specimen processing under biosafety level 2 conditions can be undertaken as is customary in most hospital laboratories. A number of disinfectants used for standard hospital infection control, such as hypochlorite, are effective in cleaning environmental surfaces contaminated with infected bodily fluids.

Proper burial or cremation of humans and animals who have died because of anthrax infection is important in preventing further transmission of the disease. Serious consideration should be given to cremation. Embalming of bodies could be associated with special risks. If autopsies are performed, all related instruments and materials should be autoclaved or incinerated. The Centers for Disease Control and Prevention can provide advice on postmortem procedures in anthrax cases.

Decontamination

Recommendations regarding decontamination in the event of an intentional aerosolization of anthrax spores are based on evidence concerning aerosolization techniques, predicted spore survival, environmental exposures at Sverdlovsk and among goat hair mill workers, and environmental data collected following the anthrax attacks of 2001. The greatest risk to humans exposed to an aerosol of Bacillus anthracis spores occurs when spores are made airborne, the period called primary aerosolization. The aerobiological factors that affect how long spores remain airborne include the size of the dispersed particles and their hydrostatic properties. Technologically sophisticated dispersal methods, such as aerosol release from military aircraft of large quantities of Bacillus anthracis spores manipulated for use in a weapon, are potentially capable of exposing high numbers of victims over large areas. Recent research by Canadian investigators has demonstrated that even "low-tech" delivery systems, such as the opening of envelopes containing powdered spores in indoor environments, can rapidly deliver high concentrations of spores to persons in the vicinity. In some circumstances, indoor airflows, activity patterns, and heating, ventilation, and air conditioning systems may transport spores to others parts of the building.

Following the period of primary aerosolization, Bacillus anthracis spores may settle on surfaces, possibly in high concentrations. The risk that Bacillus anthracis spores might pose by a process of secondary aerosolization (resuspension of spores into the air) is uncertain and is likely dependent on many variables, including the quantity of spores on a surface; the physical characteristics of the powder used in the attack; the type of surface; the nature of the human or mechanical activity that occurs in the affected area and host factors.

A variety of rapid assay kits are available to detect Bacillus anthracis spores on environmental surfaces. None of these kits has been independently evaluated or endorsed by the Centers for Disease Control and Prevention, Food and Drug Administration, or Environmental Protection Agency, and their functional characteristics are not known. Many false-positive results occurred following the anthrax attacks of 2001. Thus, any result using currently available rapid assay kits does not necessarily signify the presence of Bacillus anthracis; it is simply an indication that further testing is required by a certified microbiology laboratory. Similarly, the sensitivity and false-negative rate of disease kits are unknown.

Given the considerations discussed in the original guideline document, if an environmental surface is proved to be contaminated with Bacillus anthracis spores in the immediate area of a spill or close proximity to the point of release of Bacillus anthracis biological weapons, the working group believes that decontamination of that area would likely decrease the risk of acquiring anthrax by secondary aerosolization. However, as has been demonstrated in environmental decontamination efforts following the anthrax attacks of 2001, decontamination of buildings or parts of buildings following an anthrax attack is technically difficult. For these reasons, the working group would advise that decisions about methods for decontamination following an anthrax attack follow full expert analysis of the contaminated environment and the anthrax weapon used in the attack and be made in consultation with experts on environmental remediation. If vaccines were available, postexposure vaccination might be a useful intervention for those working in highly contaminated areas, because it could further lower the risk of anthrax infection.

In the setting of an announced alleged Bacillus anthracis release, such as the series of anthrax hoaxes occurring in many areas of the United States in 1998 and following the anthrax attacks of 2001, any person coming in direct physical contact with a substance alleged to be containing Bacillus anthracis should thoroughly wash the exposed skin and articles of clothing with soap and water. In addition, any person in direct physical contact with the alleged substance should receive postexposure antibiotic prophylaxis until the substance is proved not to be Bacillus anthracis. The anthrax attacks of 2001 and new research have shown that opening letters containing substantial quantities of Bacillus anthracis spores in certain conditions can confer risk of disease to persons at some distance from the location of where the letter was opened. For this reason, when a letter is suspected of containing (or proved to contain) Bacillus anthracis, immediate consultation with local and state public health authorities and the Centers for Disease Control and Prevention for advised medical management is warranted.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Recommendations regarding antibiotic and vaccine use in the setting of a biological anthrax attack are consensus recommendations of the Working Group based on the best available evidence (see also the "Qualifying Statements" and "Major Recommendations" fields).

Recommendations regarding decontamination in the event of an intentional aerosolization of anthrax spores are based on evidence concerning aerosolization techniques, predicted spore survival, environmental exposures at Sverdlovsk and among goat hair mill workers, and environmental data collected following the anthrax attacks of 2001.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved diagnosis, management and containment of anthrax following a bioterrorist attack

POTENTIAL HARMS

Vaccine/Vaccination

The safety of anthrax vaccine has been the subject of much study. Refer to the original guideline document for a discussion of published studies where side effects associated with of anthrax vaccine adsorbed (AVA) were reported and/or interpreted.

Antibiotic therapy and/or postexposure prophylaxis

Children

- Ciprofloxacin and other fluoroquinolones in children younger than 16 to 18 years have been linked to permanent arthropathy in adolescent animals and transient arthropathy in a small number of children.

  Note: balancing these risks against the risks of anthrax caused by an engineered antibiotic-resistant strain is considered in the guideline.

- Doxycycline used in children younger than 9 years has reportedly resulted in retarded skeletal growth in infants and discolored teeth in infants and children.

  Note: balancing these risks against the serious risk of infection following an anthrax attack is considered in the guideline.

Pregnant women

- Fluoroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals and small numbers of children.

  Note: balancing these risks against the risks of anthrax caused by an engineered antibiotic-resistant strain is considered in the guideline.

- The tetracycline class of antibiotics has been associated with both toxic effects in the liver in pregnant women and fetal toxic effects, including retarded skeletal growth.

  Note: balancing these risks against the serious risk of infection following an anthrax attack is considered in the guideline.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- In many cases, the indication and dosages and other information are not consistent with current approved labeling by the U.S. Food and Drug Administration (FDA). The recommendations on the use of drugs and vaccine for uses not approved by the Food and Drug Administration do not represent the official views of the Food and Drug Administration or of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of the original guideline document in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.
- The views, opinions, assertions, and findings contained within the original guideline document are those of the authors and should not be construed as official U.S. Department of Defense or U.S. Department of Army positions, policies, or decisions unless so designated by other documentation.
- Before the anthrax attacks in 2001, modern experience with inhalational anthrax was limited to an epidemic in Sverdlovsk, Russia, in 1979 following an unintentional release of Bacillus anthracis spores from a Soviet bioweapons factory and to 18 occupational exposure cases in the United States during the 20th century. Information about the potential impact of a large, covert attack using Bacillus anthracis or the possible efficacy of postattack vaccination or therapeutic measures remains limited. Policies and strategies continue to rely partially on interpretation and extrapolation from an incomplete and evolving knowledge base.
- Recommendations regarding antibiotic and vaccine use in the setting of a biological anthrax attack are conditioned by a limited number of studies in experimental animals, current understanding of antibiotic resistance patterns, and the possible requirement to treat large numbers of casualties. A number of possible therapeutic strategies have yet to be fully explored experimentally or submitted for approval to the Food and Drug Administration. For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not necessarily represent uses currently approved by the Food and Drug Administration or an official position on the part of any of the federal agencies whose scientists

participated in these discussions and will need to be revised as further relevant information becomes available.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Inglesby TV, O'Toole T, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Friedlander AM, Gerberding J, Hauer J, Hughes J, McDade J, Osterholm MT, Parker G, Perl TM, Russell PK, Tonat K. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002 May 1;287(17):2236-52. [114 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 May 12 (updated 2002 May 1)

GUIDELINE DEVELOPER(S)

Center for Civilian Biodefense Strategies, School of Medicine, Johns Hopkins University - Academic Institution

GUIDELINE DEVELOPER COMMENT

The working group comprised 21 representatives from academic medical centers and research, government, military, public health, and emergency management institutions and agencies, including:

- The Center for Civilian Biodefense Strategies, School of Medicine, Johns Hopkins University
- Viral and Rickettsial Diseases, California Department of Health
- U.S. Army Medical Research Institute of Infectious Diseases
- Office of Emergency Management, New York
- Centers for Disease Control and Prevention
- Acute Disease Epidemiology, Minnesota Department of Health
- Office of Emergency Preparedness, Department of Health and Human Services

SOURCE(S) OF FUNDING

Funding for the development of the working group consensus statement was primarily provided by each representative's institution or agency. The Office of Emergency Preparedness, U.S. Department of Health and Human Services (DHHS), provided travel funds for 4 members of the group.

GUIDELINE COMMITTEE

Working Group on Civilian Biodefense

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The working group included 23 experts from academic medical centers, research organizations, and governmental, military, public health, and emergency management institutions and agencies.

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Ex Officio Participants in the Working Group on Civilian Biodefense: George Curlin, MD; Margaret Hamburg, MD; Stuart Nightingale, MD; William Raub, PhD; Robert Knouss, MD; Marcelle Layton, MD; Brian Malkin

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previously issued guideline (Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon. JAMA 1999;281:1735-45).

GUIDELINE AVAILABILITY

Electronic copies: Available from the Journal of the American Medical Association Web site.

Full text available in:

- HTML Format
- Portable Document Format (PDF)

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 19, 2001. This summary was updated on May 14, 2002.

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Date Modified: 5/10/2004